Children's℠
Healthcare of Atlanta

Institutional Review Board
Phone: (404) 785-7477 Fax: (404) 785-947
irb@choa.org
http://www.choa.org/clinicalresearch

For faster processing, contact the IRB prior to submission.

EMERGENCY USE OF A TEST ARTICLE

Must be reported within 5 days of emergency use

Emergency use is defined as the use of a test article (e.g., investigational drug or biologic) on a human subject in a life-threatening situation in which no standard acceptable treatment is available and there is not sufficient time to obtain IRB approval for use. 21 CFR 50.23(a)(c), 21 CFR 50.24, 21 CFR 56.102(d)(l), 21 CFR 104(c)

REPORT TO FDA

- ***Drugs***: The physician or sponsor is responsible for submitting a new IND, or an amendment to an existing IND, to the FDA **within 15 working days** of FDA's authorization of the use. *Clearly mark as "Emergency IND".* See FDA website for Physician Request for an Individual Patient IND under Expanded Access for Non-emergency or Emergency Use; Form FDA 1571; Form FDA 1571 Instructions
- ***Devices without an IDE:*** Physician must report the use to the FDA (CDRH or CBER) ***within 5 working days.*** After a first use of the device for emergency we request that the PI evaluate the need for an IDE and provide the IRB with an update.

BASIC INFORMATION

Name of Test Article and Brief Description: CliniMacs CD34 Reagent System: Authorized by U.S. Federal law for use in the treatment of patients with acute myeloid leukemia (AML) in first complete remission; The CliniMACS® CD34 Reagent System is indicated for processing hematopoietic progenitor cells collected by apheresis (HPC, Apheresis) from an allogeneic, HLA- identical, sibling donor to obtain a CD34+ cell-enriched population for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional graft versus host disease (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) in first morphologic complete remission.			
IND/IDE #:			
Date of Use of Test Article: Approximately July 1, 2015			
An attached narrative of the situation and use of the test article must be included with the submission of this form.			
Attending Physician/PI	Dr. John Horan		
Institution	CHOA	**Department/Division**	Aflac-BMT
Phone	413-717-2542	**Email**	John.Horan@choa.org
ALTERNATE CONTACT (Coordinator/Admin Contact)	Audrey Tumlin	**Phone** **Email**	404-785-2125 Audrey.Tumlin@choa.org

EMERGENCY USE INFORMATION

Date of Use of Test Article: Approximately July 1, 2015	
Was the situation life-threatening or severely debilitating? If **yes**, please describe: Her first graft failed, leaving her with severe pancytopenia and no immune system to fight her CMV infection or other infections that arise	☒ YES ☐ NO

Is there a standard acceptable treatment available? If **no**, please describe: The patient's sibling donor is only partially HLA matched. Because of the high risk for graft versus host disease with partially matched donors, the standard measures for preventing graft versus host disease are inadequate. Several investigational measures are now being employed in this setting. CD34 selection is one strategy that has shown promise.	☐ YES ☒ NO
Was there sufficient time to obtain IRB approval? If **no**, please describe: only 8 days for approval, FDA requires 30 days	☐ YES ☒ NO
Was Informed Consent sought? **We plan to obtain informed consent from the patient and parents prior to July 1, 2015** If **yes**, please describe the consent process and provide documentation of informed consent: If **no**, provide a copy of the evaluation of PI and independent physician justifying criteria for a waiver of consent (see policy 1.60).	☐ YES ☐ NO
Is this the first use of this test article or do you plan to use this test article again in the future? If **yes**, you must complete the initial submission form and provide applicable documents. Subsequent uses of a test article typically require full and prospective IRB review or explain why an IND/IDE has not been obtained to date.	☐ YES ☒ NO
Describe subject's medical condition prior to and following treatment with the test article: PRIOR TO (will not use test article until July 1, 2015) The patient has a life threatening CMV infection. Without another transplant, she is likely to die from it in the next couple of months.	

INVESTIGATIONAL DRUG OR BIOLOGIC

If this emergency use does not involve a drug or biologic, please skip to the next section.

IND held by: ☐ **Sponsor** ☐ **Investigator**	
Manufacturer:	
Has the sponsor agreed to the use of this drug or biologic for this subject?	☐ YES ☐ NO
Has the FDA given permission for this use and this subject? If **yes**, provide FDA IND letter.	☐ YES ☐ NO

INVESTIGATIONAL DEVICE

Risk Determination: ☒ **Significant** The device removes most of the lymphocytes from the donor graft and, thereby, reduces the risk for graft versus host disease. While lymphocytes from donor are responsible for causing graft versus host disease, they also restore the patient's immune system after they go through a bone marrow transplant. The donor's lymphocytes make it possible to fight a variety of infections including CMV. CD34 selection slows the recovery of the immune function after transplant. However, this risk is relative. A transplant with CD34 selection will provide her with greater immunity than she has now. And over time, her immune function will improve. In essence the CD34 selection aims to balance the benefit and harm associated with the donor's lymphocytes by removing some, but not all of the lymphocytes. ☐ **Non-Significant**	
Manufacturer: Miltenyi Biotec	
Has the sponsor agreed to the use of this drug or biologic for this subject?	☒ YES ☐ NO
Has the FDA given permission for this use and this subject? If **yes**, provide FDA IDE letter.	☐ YES ☒ NO

ATTENDING PHYSICIAN'S SIGNATURE

The signature of the attending physician certifies that he/she acknowledges responsibility for (1) the ethical conduct of the treatment while using an emergency use test article in protecting the rights and welfare of human research subjects; (2) the timely reporting of all required information. The attending physician assures that the information in this application is correct and all procedures performed

under the Emergency Use guidelines were conducted in strict accordance with all applicable Federal, State and local regulations and laws regarding the protection of human subjects in research.

Attending Physician's Signature	Printed Name	Date
	John Horan	6-23-2015

INDEPENDENT PHYSICIAN SIGNATURE

Certification of Independent Physician Who is Not Otherwise Participating in the Investigation.

I have reviewed the information provided and certifications made by the Attending Physician/PI and certify that all of the following statements are true:

☒ The patient was confronted by a life-threatening or severely debilitating situation necessitating use of the test article.

☒ No alternative method of approved or generally recognized therapy was available that provided an equal or greater likelihood of saving the life of the patient.

☒ Informed consent was obtained OR informed consent could not be obtained because of an inability to obtain legally effective consent or parental permission.

Independent Physician's Signature	Printed Name	Date
Carlton Dampier MD	CARLTON DAMPIER MD	6/25/15

ATTACHMENT A

Institutional Review Board (IRB) Information

1. Please Provide the FWA Number assigned to the IRB that oversees clinical trial activities within your Institution:

   FWA Number: 00000644

No further information is necessary if an FWA Number is provided.

2. ***If your Institution does not have an FWA Number***, please provide the following information:

a. The IRB name, if any, used by the institution or organization (e.g., State University Behavioral IRB or University Healthcare Biomedical IRB):

_____

b. Complete Mailing Address of the IRB, including City, State and Zip; plus country if outside the USA:

_____

_____

_____

_____

c. Telephone Number(s) for IRB:

_____

_____

d. Fax Number for IRB:

_____

e. IRB Chairperson

a. Full Name: _____
b. Title or Position: _____
c. Earned Degree(s): _____

f. In lieu of providing IRB Member information in the table below, the Chairperson of the IRB may attest that the IRB is duly constituted and complies with 21 CFR parts 50 and 56. Links are as follows:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56&showFR=1

As Chairperson for the Institutional IRB referenced above in Section 2, I attest that our Institutional Review Board complies with the FDA 21 CFR Parts 50 and 56.

RESEARCH INSTITUTION Children's Healthcare of Atlanta, Inc.

DATE: 6/25/15

READ AND ACKNOWLEDGED:

INSTITUTIONAL REVIEW BOARD CHAIRMAN: (PRINT NAME) Carlton Dampier, MD

INSTITUTIONAL REVIEW BOARD CHAIRMAN (SIGNATURE) Carlton Dampier MD

If section 2.f. is <u>not</u> completed by the Chairman, please complete the table below to identify all IRB Members approving the use of the CliniMACS® CD34 Reagent System as a Humanitarian Use Device:

Member Name (Last, First)	Earned Degree(s)	Scientist (S) or Nonscientist (N)	Primary Scientific or Nonscientific Specialty	Affiliation with Institution(s) Y/N
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				

Please return this form to your Clinical Applications Manager, or Fax to 1-831-417-9621

Attachment B

(On Institutional Letterhead)

Notice of IRB Approval for the CliniMACS® CD34 Reagent System as a Humanitarian Use Device

Date:

Miltenyi Biotec Incorporated
85 Hamilton Street
Cambridge, MA 02139
Phone: 617-218-0030
Fax: 1-831-417-9621

Regarding: IRB Approval of the CliniMACS® CD34 Reagent System as a Humanitarian Use Device

To Whom It May Concern:

The letter certifies that the CliniMACS® CD34 Reagent System has been reviewed and approved by our Institutional Review Board (IRB) for Use as a Humanitarian Use Device. During the review of this Project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

It is agreed that any and all adverse event(s) that occur when using the CliniMACS® CD34 Reagent System will be reported in accordance with the Medical Device Reporting Regulations, including notification to Miltenyi Biotec Incorporated at the address and/or fax number listed above.

Signed: Carlton Dampier MD

Print Name: Carlton Dampier, MD

IRB Chairman or Treating Physician: IRB Chair

Institution: Children's Healthcare of Atlanta, Inc.

Address: 1687 Tullie Cir

Atlanta, GA 30329

Email Address: irb@choa.org

Phone: 404-785-7477

Emory University School of Medicine and Children's Healthcare of Atlanta
Consent for Transplant Treatment

Treatment Title: Infusion of Allogeneic Hematopoietic Stem Cells

Primary BMT Physician: Dr. Lakshmanan Krishnamurti

If you are the parent or legal guardian of a child who is to have a transplant, the term "you" used in this consent form means "your child."

INTRODUCTION:

We are recommending that you have an infusion of allogeneic hematopoietic blood stem cells. This is because of partial graft failure. Before you can decide whether or not to have this treatment, you must understand the treatment, how it may affect you, the risks, alternatives, and what is expected of you. This process is called informed consent.

PROCEDURES AND TREATMENT

The treatment will be done at Emory University/Children's Healthcare of Atlanta, Egleston Hospital, in the Aflac Cancer and Blood Disorders Center. A physical exam and laboratory tests will be done before the cells are given.

INFUSION OF BLOOD STEM CELLS

Blood will be collected from your sister after she has taken a medicine that causes stem cells to enter the blood from the bone marrow. . The blood collected from her will also contain white blood cells that can cause graft versus host disease. To prevent graft versus host disease, we will remove most of these white blood cells, using a technique called CD34 selection (We can tell you more about how CD34 selection works if you like).

The blood stem cells are given through the central line or IV, like a blood transfusion, over several minutes. The cells then travel to the bone marrow, where they should grow and make new blood cells. After the cells are infused, you will need to be monitored for about 4 to 6 more hours. During this time, we will treat you for side effects.

RISKS AND SIDE EFFECTS

There can be side effects of infusing blood stem cells. Most patients have few side effects during and immediately after the infusion. The side effects that do happen typically pass rapidly. . Rarely, patients can have blockage of blood vessels causing damage to organs (lungs, kidneys, brain) from small clots. In rare cases, patients have allergic reactions (may be life-threatening) or infections from the infusion.

There are also potential side effects of CD34 selection. Because it removes white blood cells, it may take many months for your immune system to get strong. During this time, you will remain more susceptible to infections. They may be life threatening.

GRAFT FAILURE AND GVHD

It is possible that the blood stem cells will not grow well in your bone marrow. This could leave you without working bone marrow cells, which may cause life-threatening complications. It is also possible that even with the CD34 selection, you may still get graft versus host disease.

WHAT WILL BE DONE TO MINIMIZE RISKS

You will be given medications before the infusion to try and prevent these reactions. Your BMT doctor and staff will be checking closely to see if any of these side effects are happening. If possible, we will try to prevent undesirable side effects. If they happen, we will give treatment to control them, such as medication for nausea.

Your doctors and nurses will watch you carefully for infection. They will use medicines and other treatments to try and prevent infections. If you develop infections, they will treat you. These treatments, though, do not always work.

ALTERNATIVES TO THIS TREATMENT

You may choose not to have the infusion of blood stem cells. Please discuss all the options with your doctors, and ask all of the questions that you have. Alternatives include:

- Not having the blood stem cells infused, but getting supportive care such as antibiotics to treat infections and blood transfusions for low blood counts.
- Research studies with new treatments; if available (your doctor can discuss what may be available for you).

CONTACT PERSONS

If you have any questions about this treatment, contact your BMT physician. If you believe you have been injured by this treatment, you should contact your BMT physician.

SIGNATURE FOR DOCUMENTATION OF CONSENT

We will give you a copy of this consent form to keep.
If you agree to this treatment, please sign below.

_____
Print patient's name

_____ _____ _____
Patient, Parent or legal guardian ***Date*** ***Time***

_____ _____ _____
Person Obtaining Consent ***Date*** ***Time***

Miltenyi Biotec

85 Hamilton Street
Cambridge, MA 02139
Phone: 617-218-0030
Fax: 617-218-0050

February 10, 2014

Dear CliniMACS® System IDE/IND Holder:

By now you have no doubt heard the exciting news regarding the FDA approval of the CliniMACS® CD34 Reagent System. Attached you will find the January 23, 2014 Approval Order from FDA, the Instructions for Use (IFU), and the letter, "CliniMACS® CD34 Reagent System HUD – requirements for commercial distribution", that provides additional information about the Humanitarian Device Approval, including the requirements for use in the absence of a protocol under an FDA approved IDE/IND. Additionally, the aforementioned letter also provides answers to commonly asked questions that you may have regarding the use of the FDA approvedCliniMACS® CD34 Reagent System.

Since you currently have an open protocol(s) that uses the CliniMACS® CD34 Reagent System, we want to provide some additional clarification on how this approval will impact your trial(s) going forward.

1. As you will see in the bolded paragraph on page 3 of the attached letter, "CliniMACS® CD34 Reagent System HUD – requirements for commercial distribution", the CliniMACS® CD34 Reagent, CliniMACS® Tubing Sets and CliniMACS® PBS/EDTA Buffer will continue to be shipped to your Institution as long as we have the necessary documentation indicating that the trial has been approved by both your IRB AND the FDA. You must continue to reference the IND or IDE number when ordering product as you have in the past, as long as your FDA sanctioned trial remains active.

2. The labeling on the consumable products that you have been ordering/receiving will change in the March timeframe. The CliniMACS® CD34 Reagent will have a new package insert, and an Instructions for Use (IFU) that summarizes the HDE indication and usage information. The Tubing Sets (TS and LS) and Buffer will have generic labeling, enabling these products for use with the HDE approved CliniMACS® CD34 Reagent System, as well as for use with other types of CliniMACS® Reagents used under FDA sanctioned IND or IDE protocols. The Tubing Sets (TS and LS) and Buffer labeling will no longer specify that they are for investigational use. If your Institution/protocol requires this, you may need to add an additional label to the product specifying their use as an investigational device.

3. Since the CliniMACS® CD34 Reagent will soon be labeled only as a Humanitarian Use Device, the FDA has asked that we encourage customers to maintain internal records or storage systems for products that are used in accordance with the HDE requirements (IRB sanctioned only) versus those that are used in investigational protocols (IRB and FDA sanctioned protocols).

4. In the near future, Miltenyi will be generating a replacement IDE labeled CliniMACS® CD34 Reagent, which may be shipped to customers who provide documentation that the protocol has been sanctioned by both the IRB and FDA, much like we have historically done. The ongoing shipment of HDE labeled product only requires our receipt of the IRB approval documents provided in Attachments A & B of the letter "CliniMACS® CD34 Reagent System HUD – requirements for commercial distribution".

We are ready to support you in integrating the newly approved CliniMACS® CD34 Reagent System into your clinical practice! Please do not hesitate to contact your Miltenyi Clinical Applications Manager or myself if we can provide additional information in support of your future needs.

Sincerely,

Tara Clark

Tara Clark
General Manager, N.A. Clinical Operations
Miltenyi Biotec, Inc.
85 Hamilton Street
Cambridge, MA 02139
617-218-0061
tclark@miltenyibiotec.com

Attachments: January 23, 2014 FDA Approval Order for the CliniMACS® CD34 Reagent System
IFU- CliniMACS® CD34 Reagent System
CliniMACS CD34 Reagent System HUD – requirements for commercial distribution

Vaccines, Blood & Biologics

January 23, 2014 Approval Order - CliniMACS® CD34 Reagent System

Miltenyi Biotech, Inc.
Attention: Nancy Johansen
120 Presidential Way, Suite 305
Woburn, MA 01801

Re: **HDE Number:** BH110018
HUD Number: 04-0146
Device Name: CliniMACS® CD34 Reagent System
Filed: May 10, 2011
Amended: June 14, July 5, July 20, July 26, August 9, August 10, September 12, October 3, October 17, October 27, December 16, and December 28, 2011; May 29, June 7, July 16, July 23, and December 21, 2012; February 19, February 25, March 7, April 1, April 2, April 3, May 15, May 20, May 24, July 2, July 16, July 26, and December 3, 2013; January 2 and January 10, 2014
Product Code: OVG

Dear Ms. Johansen:

The Center for Biologics Evaluation and Research of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for the CliniMACS® CD34 Reagent System. This device is indicated for processing hematopoietic progenitor cells collected by apheresis (HPC, Apheresis) from an allogeneic, HLA-identical, sibling donor to obtain a $CD34^+$ cell-enriched population for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional graft versus host disease (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) in first morphologic complete remission. We are pleased to inform you that your HDE is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale, distribution, and use of this device are limited to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) under the authority of section 515(d)(1)(B)(ii) of the FD&C Act. In addition, in order to ensure the safe use of the device, FDA has further restricted the device within the meaning of section 520(e) of the FD&C Act under the authority of section 515(d)(1)(B)(ii) of the FD&C Act insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the FD&C Act.

The components of the CliniMACS® CD34 Reagent System are the CliniMACS® CD34 Reagent, CliniMACS® plus Instrument (Model CS2-CE/UI), CliniMACS® Tubing Set (Standard (TS) or Large Scale (LS)), and CliniMACS® PBS/EDTA Buffer. Expiration dating for the components and intermediates has been established and approved as follows:

- Final Filled CliniMACS® CD34 Reagent: 18 months when stored at -70°C followed by 6 months when stored at 2-8°C
- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------
- CliniMACS® Tubing Set: 35 months from the date of sterilization
- CliniMACS® PBS/EDTA Buffer: 35 months from the date of sterilization

Continued approval of this HDE is contingent upon the submission of periodic reports, required under 21 CFR 814.126, at intervals of one year (unless otherwise specified) from the date of approval of the original HDE. Two (2) copies of this report, identified as "Annual Report"and bearing the applicable HDE reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.126.

In addition to the above, an HDE holder is required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

You have agreed to the following post-approval conditions:

Cleaning validation

1. Miltenyi Biotec will use ----------(b)(4)---------- that meets -(b)(4)- specifications to repeat the cleaning validation for the multi-use product contact equipment used to manufacture CliniMACS CD34 Reagent System at Miltenyi's Branch -(b)(4)-- Facility in --(b)(4)--. Miltenyi Biotec will submit the results of the executed cleaning validation by June 30, 2014.

2. Miltenyi Biotec will conduct periodic cleaning verifications to ensure that the cleaning procedures are still effective. Miltenyi Biotec will submit the updated SOP documenting cleaning verification procedures by June 30, 2014.

---------(b)(4)------- testing of the CD34 Reagent

3. Miltenyi Biotec will confirm the specificity/sensitivity of the commercial --(b)(4)---------- will be submitted by June 30, 2014.

4. Miltenyi Biotec will develop and validate a process-specific ----------(b)(4)---------- if the specificity/sensitivity of the ----------(b)(4)---------- cannot be adequately demonstrated. The final study and validation reports will be submitted by June 30, 2014.

Stability of the CD34 Reagent

5. Miltenyi Biotec will submit annually the stability data from ongoing stability protocols for the ----------(b)(4)----------, and CliniMACS® CD34 Final Filled Reagent. In addition, at least one commercial lot of each will be added to the stability program every year a lot is manufactured and these data will be submitted annually.

User Training

6. Miltenyi Biotec will provide user training as described in SOP-1862 "Training of CliniMACS® Users (Customers) for Miltenyi Biotec Inc. (US)". Miltenyi Biotec will seek FDA approval prior to significant modification of this SOP and the user training program.

Before making any change affecting the safety or effectiveness of the device, you must submit an HDE supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39 except a request for a new indication for use of for a humanitarian use device (HUD). A request for a new indication for use for an HUD shall comply with the requirements set forth in 21 CFR 814.110 which includes obtaining a new designation of HUD status for the new indication for use and submission of an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise become aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm[1].

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm[2].

This device may not be sold for an amount that exceeds the costs of research and development, fabrication, and distribution of the device. See section 520(m)(3) of the Federal Food, Drug, and Cosmetic Act.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of an HDE. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

CBER does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading. CBER will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CBER Internet Page located at http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm089793.htm[3]. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the FD&C Act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this HDE submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when HDE applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Attn: Office of Cellular, Tissue, and Gene Therapies
Document Control Center, HFM-99, Suite 200N
1401 Rockville Pike
Rockville, MD 20852-1448

If you have any questions concerning this approval order, please contact Candace Jarvis at (301) -827-6536.

Sincerely yours,

Celia M. Witten, Ph.D., M.D.
Director
Office of Cellular, Tissue and Gene Therapies
Center for Biologics Evaluation and Research

Page Last Updated: 01/27/2014
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
Accessibility Contact FDA Careers FDA Basics FOIA No Fear Act Site Map Transparency Website Policies

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

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U.S. Department of **Health & Human Services**

Links on this page:

1. http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm
2. http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm
3. http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm089793.htm

CliniMACS® CD34 Reagent System

Rx only

For *in vitro* use only.

HUMANITARIAN DEVICE:

Authorized by U.S. Federal law for use in the treatment of patients with acute myeloid leukemia (AML) in first complete remission. The effectiveness of the device for this use has not been demonstrated.

MANUFACTURED BY:
Miltenyi Biotec GmbH
Friedrich-Ebert-Straße 68
D 51429 Bergisch Gladbach | Germany
Phone: +49 2204 8306-80
Fax:+49 2204 85197

DISTRIBUTED IN THE US BY:
Miltenyi Biotec Inc.
2303 Lindbergh Street | Auburn, CA 95602
Phone: 1 800 367 6227

INDICATIONS FOR USE

The CliniMACS® CD34 Reagent System is indicated for processing hematopoietic progenitor cells collected by apheresis (HPC, Apheresis) from an allogeneic, HLA-identical, sibling donor to obtain a $CD34^+$ cell-enriched population for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional graft versus host disease (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) in first morphologic complete remission.

CONTRAINDICATIONS

Do not use $CD34^+$ cells prepared with CliniMACS® CD34 Reagent System in patients with known hypersensitivity to murine (mouse) proteins or iron-dextran.

DESCRIPTION

The CliniMACS® CD34 Reagent System is a medical device system that consists of the following components:

- CliniMACS® CD34 Reagent - dark amber, non-viscous, colloidal solution containing an antibody conjugate in buffer. The conjugate consists of a murine IgG_1 monoclonal antibody directed against the Class II epitope of the human CD34 antigen, which is chemically conjugated to dextran beads having an iron oxide/hydroxide core. (See the CliniMACS® CD34 Reagent Package Insert for more information.)
- CliniMACS® plus Instrument - software-controlled instrument that processes the HPC, Apheresis. (See the CliniMACS® User Manual for the CD34 Reagent System for more information.)
- CliniMACS® Tubing Set TS or Tubing Set LS - a single-use, sterile, disposable tubing set with two proprietary cell separation columns. The CliniMACS® Tubing Set TS is for processing HPC, Apheresis preparations containing up to 0.6×10^9 $CD34^+$ cells out of a total cell number not exceeding 60×10^9 white blood cells. The CliniMACS® Tubing Set LS is for larger scale preparations containing up to 1.2×10^9 $CD34^+$ cells out of a total cell number not exceeding 120×10^9 white blood cells. (See the CliniMACS® Tubing Sets Package Insert and the CliniMACS® User Manual for the CD34 Reagent System for more information.)
- CliniMACS® PBS/EDTA Buffer - a sterile, isotonic phosphate-buffered, 1 mM EDTA, saline solution, used as external wash and transport fluid for the *in vitro* processing of HPC, Apheresis. (See the CliniMACS® PBS/EDTA Buffer Package Insert and the CliniMACS® User Manual for the CD34 Reagent System for more information.)

PRINCIPLES OF OPERATION

The CliniMACS® CD34 Reagent System is an *in vitro* medical device system used to select and enrich $CD34^+$ cells from HPC, Apheresis while passively depleting other cells, such as $CD3^+$ T cells, which cause graft versus host disease. The system is based on "magnetically-activated cell sorting" (MACS) employing antibodies conjugated to iron-containing particles that can be attracted to a magnetic field (referred to as "magnetic labeling"). Using the specificity of anti-CD34 antibody interaction with cell surface CD34 antigen found on hematopoietic progenitor cells, the system enriches $CD34^+$ cells from HPC, Apheresis by passing the antibody-labeled cell suspension through a separation column with a strong magnetic gradient. The separation column retains the magnetically labeled $CD34^+$ target cells while unlabeled cells flow through and are collected in the Negative Fraction Bag. Several automated washing steps are performed, disposing most of the liquid into the Buffer Waste Bag. The magnetically-selected $CD34^+$ cells are released from the separation column when the magnet is disengaged, removing the magnetic field, and the target $CD34^+$ cells are eluted into the Cell Collection Bag.

WARNINGS

- Do not infuse the CliniMACS® CD34 Reagent or the CliniMACS® PBS/EDTA Buffer into patients directly.
- Hypersensitivity Reactions

  Hypersensitivity reactions, including anaphylaxis, have been observed during infusion of $CD34^+$ cells from the CliniMACS® CD34 Reagent System. Monitor the patient for hypersensitivity reactions, including anaphylaxis, during infusion of $CD34^+$ cells from the CliniMACS® CD34 Reagent System.
- Engraftment failure

  Failure to infuse an adequate number of functioning $CD34^+$ cells can result in engraftment failure. Collect sufficient HPC, Apheresis to yield at least 2.4×10^6 $CD34^+$ cells per kg of patient body weight after system processing (see Device Performance below). The clinical trial (see Clinical Performance below) using the CliniMACS® CD34 Reagent System to process HPC, Apheresis did not test allografts with less than 2.4×10^6 $CD34^+$ cells per kg of recipient body weight. Monitor patients for laboratory evidence of hematopoietic recovery after transplantation.
- Acute and chronic graft versus host disease (GVHD)

  GVHD can occur in patients who receive HPC, Apheresis processed using the CliniMACS® CD34 Reagent System. Use pharmacologic prophylaxis if more than 1×10^5 $CD3^+$ cells per kilogram of recipient body weight are infused.
- Delayed immune reconstitution after transplantation

  Removal of T cells from the HPC, Apheresis can delay immune reconstitution after transplantation. Patients who receive the $CD34^+$ cell-enriched population prepared using the CliniMACS® CD34 Reagent System are at risk for serious opportunistic viral infections, including post-transplant lymphoproliferative disorder caused by Epstein-Barr virus (EBV) and cytomegalovirus (CMV). Monitor for EBV and CMV in the peripheral blood of patients after transplantation and initiate appropriate treatment promptly.

PRECAUTIONS

- Safety and probable benefit in children under the age of 17 years have not been established.
- Drugs may be incompatible with the CliniMACS® PBS/EDTA Buffer. Do not add drugs to the buffer other than Human Serum Albumin as specified in the CliniMACS® User Manual for the CD34 Reagent System.
- Do not use cryopreserved and thawed HPC, Apheresis because cryopreservation promotes cell clumping, which may lead to device performance issues. Process HPC, Apheresis as soon as available, but not longer than 24 hours after collection.
- Use only HPC, Apheresis from an allogeneic, HLA-identical sibling donor with the CliniMACS® CD34 Reagent System.
- Collect HPC, Apheresis according to standard hospital or institutional leukapheresis procedures in standard leukapheresis collection bags. Do not include additional anticoagulants or blood additives, such as heparin, other than those normally used during leukapheresis. Keep the HPC, Apheresis at controlled room temperature (+19 °C to +25 °C (67° to 77° F)) if it has to be stored, e.g., overnight, before processing. Do not allow the concentration of leukocytes to exceed 0.2×10^9 cells per mL.
- Only trained operators should use the CliniMACS® CD34 Reagent System to prepare $CD34^+$ cells for infusion. Operator training is provided by Miltenyi Biotec authorized personnel.

PROCEDURES

Refer to the CliniMACS® User Manual for the CD34 Reagent System for complete instructions. An on-line version is available at www.cd34-aml.com/usermanual.

Do not connect the CliniMACS® CD34 Reagent System to the patient at any time.

Collect the following data on the leukapheresis product before starting the preparation of the HPC, Apheresis for enrichment:

- Total number of leukocytes
- Percentage of $CD34^+$ cells
- Total number of $CD34^+$ cells
- Percentage of $CD3^+$ cells
- Total number of $CD3^+$ cells
- Viability

The $CD34^+$ cells are enriched in the following four steps:

Step 1 - Immunomagnetic Labeling of $CD34^+$ Hematopoietic Progenitor Cells

Add the CliniMACS® CD34 Reagent to the HPC, Apheresis and allow the reagent to bind to the $CD34^+$ cells. After incubation, remove unbound reagent from the suspension. The cells are now ready for selection in an automated continuous flow selection process using the CliniMACS® plus Instrument.

NOTE: Exceeding the capacity for either total cell number or $CD34^+$ cell number may impact the performance of the device. The standard-scale capacity for the enrichment of $CD34^+$ cells using the CliniMACS® CD34 Reagent System with one vial of CD34 Reagent and the CliniMACS® Tubing Set TS is 0.6×10^9 $CD34^+$ cells out of a total cell number not exceeding 60×10^9 cells. Large-scale capacity for the enrichment of up to 1.2×10^9 $CD34^+$ cells out of a total cell number of 120×10^9 cells (large-scale application) requires two vials of the CliniMACS® CD34 Reagent and the CliniMACS® Tubing Set LS.

Step 2 - Choice of Program

Choose CD34 Selection 1/2 program on the CliniMACS® plus Instrument.

Step 3 - Installation of Tubing Set

- Install tubing set (TS or LS).
- Attach Cell Collection Bag to the tubing set.
- Follow the prompts provided on the CliniMACS® plus Instrument screen to complete the tubing set installation.
- Join the bag containing the cells from Step 1 to the sterile CliniMACS® Tubing Set.

Step 4 - Selection of CD34+ Cells

Process the cells through the CliniMACS® plus Instrument using the CD34 Selection program. The instrument selects cells by passing the immunomagnetically-labeled suspension through the separation column, in which strong magnetic gradients are generated. The separation column retains the immunomagnetically-labeled $CD34^+$ target cells while unlabeled cells flow through and are collected in the Negative Fraction Bag. Automated washing steps dispose of excess liquid into the Buffer Waste Bag. The retained $CD34^+$ cells are released from the separation column when the magnet is disengaged, and the target $CD34^+$ cells are eluted into the Cell Collection Bag.

Establish the suitability of the target $CD34^+$ cells before infusion. Examine the following parameters:

- Total number of leukocytes
- Total viability
- Total number of $CD34^+$ cells
- Total number $CD3^+$ cells
- Purity and recovery of $CD34^+$ cells
- CD3 log depletion

See Table 1 for performance values observed in the clinical trial.

Assessment of the non-target fraction for the total number and viability of leukocytes is recommended to assess the performance of the device and quality of the device output ($CD34^+$ cells).

DO NOT infuse the $CD34^+$ cells in CliniMACS® PBS/EDTA Buffer! Exchange the CliniMACS® PBS/EDTA Buffer contained in the $CD34^+$ target fraction to a clinical grade infusion solution appropriate for infusion into humans prior to infusion of the $CD34^+$ cells.

See the CliniMACS® User Manual for the CD34 Reagent System for full instructions. The CliniMACS® User Manual for the CD34 Reagent System includes instructions on the preparation of solutions and samples, as well as a detailed list of equipment and materials that are required for $CD34^+$ cell selection. (See Chapter 3 of the CliniMACS® User Manual for the CD34 Reagent System.)

PERFORMANCE CHARACTERISTICS

Adverse Reactions

The safety of the CliniMACS® CD34 Reagent System was evaluated in a clinical trial that included 44 subjects with AML undergoing HPC, Apheresis transplantation from an HLA-identical sibling donor.[1] There were 16 males and 28 females of median age 49 years (range, 21 to 60 years). The myeloablative preparative regimen included total body irradiation, thiotepa, cyclophosphamide, and rabbit antithymocyte globulin. The median number of $CD34^+$ cells infused was 7.9×10^6 per kg (range 2.4 to 30 4). The median number of $CD3^+$ cells infused was 0.07×10^5 per kg (range 0.01 to 0.83).

Among the 44 subjects, there were no grades 3 to 5 infusion reactions, no allergic reactions, and no graft failures. Testing for development of human anti-mouse antibodies (HAMA) was not performed. A severe or life-threatening infection was reported for 38% of the subjects. An infection by any virus was reported for 61% of the subjects, and the 1-year incidence of EBV infection in particular was 25%. One subject (2%) developed a fatal post-transplantation lymphoproliferative disorder.

Device Performance

The safety and feasibility of use of the CliniMACS® CD34 Reagent System was evaluated in a multicenter, single-arm, clinical trial. In this study, allogeneic donors were mobilized with daily subcutaneous granulocyte colony-stimulating factor (G-CSF) at a dose of 10 to 16 µg per kg per day. Leukapheresis was performed on a continuous flow cell separator commencing on Day 5 of G-CSF treatment, and $CD34^+$ cell enrichment of the HPC, Apheresis was performed using the CliniMACS® CD34 Reagent System. Most donors underwent at least two, but not more than three, aphereses to reach the post-selection enrichment target of greater than 5.0×10^6 $CD34^+$ cells per kg recipient body weight while maintaining less than 1.0×10^5 $CD3^+$ cells per kg recipient body weight.

Eighty-four selection procedures were performed on HPC, Apheresis collected from a total of 44 donors. The minimum number of $CD34^+$ cells required for transplantation, greater than 2×10^6 per kg recipient body weight, was achieved for 100% (44) of donors. This was attained with one apheresis for 93% (41) of the donors and two aphereses for an additional 7% (3). The target number of $CD34^+$ cells, greater than 5×10^6 per kg recipient body weight, was achieved for 84% (37) of the 44 donors. This target number was attained with one apheresis for 36% (16), with two aphereses for 45% (20), and with three aphereses for 2% (1) of the 44 donors. Device performance is shown in the table below.

Table 1: Device Performance Summary; N=84

Attributes Measured		Mean	Std Dev	Median	Min	Max
Starting TNC $\times 10^{10}$		7.46	3.26	6.95	2.1	18.0
Initial Viability (%)		97.60	2.74	99.0	86.9	100.0
$CD34^+$ Cells $\times 10^7$	Starting Count	59.71	41.09	47.85	7.3	208.0
	Final Count	36.90	25.05	29.80	6.1	119.0
Final $CD34^+$ Yield (%)		66.06	20.25	65.00	29.9	125.6
Final $CD34^+$ Purity (%)		93.03	8.31	96.65	61.5	99.8
$CD3^+$ T Cells $\times 10^8$	Starting Count	179.45	69.80	168.50	55.00	362.00
	Final Count	0.00652	0.01039	0.00217	0.00026	0.04971
Log_{10} $CD3^+$ T-Cell Depletion		4.78	0.55	4.90	3.2	5.9
Final Viability (%)		96.57	3.84	97.70	74.0	100.0
Total $CD34^+$ Cells Infused/kg $\times 10^6$		8.81	5.21	7.924	2.41	30.360
Total $CD3^+$ Cells Infused/kg $\times 10^6$		0.015	0.020	0.0066	0.0011	0.08328

Clinical Performance

The clinical trial included 37 subjects with AML in first complete remission (CR) undergoing transplantation. All donors were HLA-identical siblings. The study subjects included 14 (37.8%) males and 23 (62.2%) females of median age 48 years (range: 21 to 60 years). The cytogenetics risk group was intermediate for 68%, unfavorable for 27%, and unknown for 5% of subjects. The myeloablative preparative regimen included total body irradiation, thiotepa, cyclophosphamide, and rabbit antithymocyte globulin. The median number of $CD34^+$ cells infused was 7.4×10^6 per kg recipient body weight (range: 2.4 to 30.4). The median number of $CD3^+$ cells infused was 0.07×10^5 per kg recipient body weight (range: 0.01 to 0.63). No immunosuppressive drugs were administered for prevention of GVHD.

All subjects achieved an absolute neutrophil count that exceeded 0.5×10^9 per liter by Day 21 after transplantation. The platelet count recovered to greater than 20×10^9 per liter by Day 100 for 91.9% (95% CI, 82.4 to 100%). There was one late graft failure. At Day 100 after transplantation, the cumulative incidence of grades 2 to 4 acute GVHD was 27% (95% CI, 14 to 42%), and that for grades 3 to 4 acute GVHD was 5% (95% CI, 1 to 16%). The cumulative incidence of chronic GVHD at 2 years after transplantation was 19% (95% CI, 8 to 33%).

Additional Safety Assessment

The potential risks of using the CliniMACS® CD34 Reagent System were evaluated via a Data Analysis Protocol (DAP), which retrospectively compared the Day-100, 1-year, and 2-year endpoints in the clinical trial to the same endpoints as had been measured in a historical control group of patients that had used a conventional pharmacologic method of GVHD prophylaxis. Table 2 shows the results of the comparison.

Table 2: Comparison of the Single-Arm CliniMACS® CD34 Reagent System Study to historical controls using pharmacological immunosuppression

Endpoints	Single-Arm CliniMACS® CD34 Reagent System (n=37) % (95% CI)	Historical Controls Using pharmacological immunosuppression (n=65) % (95% CI)
% Neutrophil Engraftment at Day 30 (>500/µL)*	100	100[‡]
% Platelet Engraftment at Day 30 (>20,000/µL)*	92 (82.4, 100)	84[#](72.5, 91.4)
Acute GVHD at Day 100, Grades 2–4*	27 (13.9, 42.0)	35 (23.9, 47.0)
Acute GVHD at Day 100, Grades 3–4*	5 (1, 16.1)	9 (3.7, 17.8)
Chronic GVHD at 2 years*	19 (8.2, 33.0)	49 (36.5, 61.0)
Relapse Rate at 2 years*	16 (6.5, 29.9)	28 (17.7, 39.7)
Non-relapse Mortality at 2 years*	20 (8.5, 34.5)	14 (6.8, 23.4)
Overall Survival at 2 years	67 (48.8, 79.7)	67 (54.1, 77.2)
Disease-free Survival at 2 years	64 (46.0, 77.4)	58 (44.8, 68.9)
GVHD-free Survival at 2 years	46 (29.6, 60.9)	18 (9.6, 28.2)

* Cumulative Incidence
‡ neutrophil engraftment data missing for two patients
# Platelet data missing for one patient

REFERENCES

1 Devine SM, Carter S, Soiffer RJ, Pasquini MC, Hari PN, Stein A, Lazarus HM, Linker C, Stadtmauer EA, Alyea EP 3rd, Keever-Taylor CA, O'Reilly RJ. Low Risk of Chronic Graft-versus-Host Disease and Relapse Associated with T Cell-Depleted Peripheral Blood Stem Cell Transplantation for Acute Myelogenous Leukemia in First Remission: Results of the Blood and Marrow Transplant Clinical Trials Network Protocol 0303. Biology of Blood and Marrow Transplantation 2011;17:1343-1351

Miltenyi Biotec

85 Hamilton Street
Cambridge, MA 02139
Phone: 617-218-0030
Fax: 617-218-0050

February 10, 2014

Subject: CliniMACS® CD34 Reagent System HUD – Requirements for commercial distribution

Dear Doctor:

On January 23, 2014, Miltenyi Biotec's CliniMACS® CD34 Reagent System was approved as a Humanitarian Use Device (HUD) by the U.S. FDA following Miltenyi's submission pursuant to regulations outlined in the Humanitarian Device Exemption (HDE) regulations. The approved label indication is as follows:

HUMANITARIAN DEVICE: Authorized by U.S. Federal law for use in the treatment of patients with acute myeloid leukemia (AML) in first complete remission. The effectiveness of the device for this indication has not been demonstrated.

INDICATIONS AND USAGE

The CliniMACS® CD34 Reagent System is indicated for processing hematopoietic progenitor cells collected by apheresis (HPC, Apheresis) from an allogeneic, HLA-identical, sibling donor to obtain a $CD34^+$ cell-enriched population for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional graft versus host disease (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) in first morphologic complete remission.

What does "the effectiveness of the device for this indication has not been demonstrated" mean?

A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. The number of patients diagnosed with AML in CR1, and indicated for allogeneic transplantation, enables the CliniMACS® CD34 Reagent System to be regulated and approved as an HUD.

The Humanitarian Device Exemption (HDE) regulatory submission is similar in both format and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. Given the low patient numbers, an HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is ***effective*** for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury. Furthermore, the clinical data must support a premise of "probable benefit"; in that the risk to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. The CliniMACS® CD34 Reagent System was shown to meet this requirement.

What does this mean for me?

The CliniMACS® CD34 Reagent System is now available for sale under the HDE regulations. The following components now have the HDE indication on their package insert:

CliniMACS® CD34 Reagent (200-070-103)
CliniMACS® PBS/EDTA Buffer (200-070-026)
CliniMACS® Tubing Set TS (200-073-105) and Tubing Set LS (200-070-205)
CliniMACS® plus Instrument (200-029-101)

What is required in order for me to use the CliniMACS® CD34 Reagent System?

Unlike our procedures surrounding the distribution of other Investigational Products, the purchase of the above components will no longer require documentation from FDA.. However, as the holder of the HDE for the CliniMACS® CD34 Reagent System, Miltenyi Biotec is responsible for ensuring that the CliniMACS CD34 Reagent System is:

1. **used under physician order, only in Institutions having a properly constituted and functioning Institutional Review Board (IRB) and**
2. **The IRB has approved the use of this Humanitarian Use Device in treating patients within the Institution.**

Documentation confirming both of these requirements must be in place at Miltenyi Biotec in order for the CliniMACS® CD34 Reagent System components to be shipped to your Institution.

Requirement #1: How does Miltenyi plan to ascertain that Institutions have a properly constituted IRB?

Pursuant to 45 CFR Part 46, the U.S. Department of Health and Human Services (www.hhs.gov) has oversight of "Office for Human Research Protection" (OHRP) which assigns **Federal-wide Assurance (FWA) numbers.** Through the FWA, an Institution commits to HHS that it will comply with the requirements for the Protection of Human Subjects per 21 CFR Parts 50 and 56. Thus, Miltenyi Biotec intends to use the FWA numbers to certify that each Institution that receives HDE product operates under a properly constituted and functioning IRB.

All existing, and future sites wishing to utilize the CliniMACS CD34 Reagent System as a Humanitarian Use Device will be asked to provide their FWA number to Miltenyi Biotec to satisfy that they operate under a properly constituted and functioning IRB. The information supplied in **Attachment A** will be filed by Miltenyi Biotec in order to satisfy requirement #1 listed above. If the IRB which oversees the use of the CliniMACS CD34 Reagent System site does **not** have an FWA number, the Institution will be required instead, to submit responses to the questions listed under Item #2 of **Attachment A or provide an equivalent formal written attestation of this information.** Miltenyi Biotec must receive the information listed under #1 or #2 of **Attachment A** in order for the CliniMACS CD34 Reagent System components to be provided to your Institution without an FDA assigned IND or IDE number.

Requirement #2: What must my IRB do to review and approve the use of the CliniMACS CD34 Reagent System as a Humanitarian Use Device?

The CliniMACS® CD34 Reagent System has been approved for marketing within the indication listed above. This FDA approval is based on evidence of safety and probable benefit within the patient population treated in the clinical study. Therefore, the use of the System to treat the patients meeting the approved indication is not deemed "clinical investigation". Even though the device is not considered investigational, IRB review is required per the Humanitarian Use Device Regulations,

with the exception of emergency use. The initial review must be performed by the full Institutional Review Board, although continuations may be performed by expedited review.

The health care provider(s) at the Institution continue to be responsible for obtaining IRB approval before using the CliniMACS® CD34 Reagent System as a Humanitarian Use Device (HUD), except in certain emergencies where prior IRB approval is not required. Specifically, FDA recommends reviewing the following materials during initial review of the HUD. The first **TWO** items will be provided by Miltenyi Biotec:

- A copy of the January 23, 2014 Approval Order – CliniMACS® CD34 Reagent System
- The CliniMACS® CD34 Reagent System Instructions for Use (IFU)
- A summary of how the physician(s) within the Institution propose to use the System, including a description of the inclusion criteria.

Currently, many IRBs provide guidance and/or forms for HUD or HDE applications to the IRB. While the HDE regulations do not require informed consent for treating patients within the label indication, it is up to your Institution as to whether a patient consent will be required.

In reviewing the use of the CliniMACS® CD34 Reagent System as a HUD, your IRB should understand that the FDA has made a determination of safety and probable benefit for use of the HUD within its approved indication. The IRB is not required to review and approve each individual use. Your IRB may use its discretion to determine how to approve use of a HUD. When a HUD is used to treat patients, i.e., not for research, the FDA does not require submission of a protocol to the IRB for review. However, your IRB or Institution may require one under its own policies and procedures.

There is no regulatory requirement for committees other than the IRB to approve the use of a HUD. However, this is left to the discretion of your Institution. Similarly, the FDA does not require you to audit medical records of patients who have been treated using a HUD.

Am I required to obtain IRB Approval for use of the HUD if our Institution already has an approved protocol for the use of the CliniMACS CD34 Reagent System under the Investigational Device Exemption (IDE) Regulations ?

Yes. The labeling has changed on all components of the CliniMACS CD34 Reagent System to reflect the new Indication as a Humanitarian Use Device. According to the FDA requirements if the initial review was performed using the full panel, IRBs may use the expedited review procedure as outlined in 21CFR 56.110. FDA recommends the use of an expedited procedure because a HUD is a legally marketed device and no safety and effectiveness information is being collected, as is required for research protocols. An expedited review does not mean a less than substantive review. During the expedited review, the Chair or the Chair's designated member(s) should thoughtfully consider the risk and benefit information. IRBs may develop their own policies and procedures for continuing review of a HUD and may perform this review at a convened meeting.

In accordance with this FDA Guidance, Miltenyi is required to document proof that your Institution's IRB has approved the use of the CliniMACS CD34 Reagent System as a Humanitarian Use Device in order for product to be shipped to your Institution without documented proof of an FDA sanctioned protocol. Once you have obtained IRB Approval to use the System, please complete Attachment B or an equivalent attestation, and forward this information to your Clinical Applications Manager or myself. Taken with the Information

provided in Attachment A, you will then be able to routinely order the CliniMACS CD34 Reagent, Tubing Sets and Buffer.

Will Miltenyi ship product if I have a patient requiring emergent therapy and I do not yet have IRB approval?

Yes. If you as a physician are treating in an emergency situation and determine that IRB approval for the use of the CliniMACS® CD34 Reagent System cannot be obtained in time to prevent serious harm or death to a patient, the CliniMACS® CD34 Reagent System may be used without prior IRB approval. You should contact your Clinical Applications Manager, or myself and we will arrange for product to be shipped for you on a "emergency" basis. You must however, provide written notification regarding the emergency use to your IRB Chairman within five days; including identification of the patient involved, the date of the use, and the reason for the emergency use.

Please refer to the FDA Guidance: "Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers" for additional information regarding IRB review of Humanitarian Use Devices:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm#7

We are anxious to support the integration of the newly approved CliniMACS® CD34 Reagent System into your clinical practice! Please do not hesitate to contact your Miltenyi Clinical Applications Manager at our toll free number, 1-800-FOR-MACS (1-530-888-8871) Prompt #5, or myself if we can provide additional information in support of your IRB application.

Sincerely,

Tara Clark

Tara Clark
General Manager, N.A. Clinical Operations
Miltenyi Biotec, Inc.
85 Hamilton Street
Cambridge, MA 02139
617-218-0061
tclark@miltenyibiotec.com

Attachments: A: Institutional Review Board (IRB) Information
B: Notice of IRB Approval for the CliniMACS® CD34 Reagent System as a Humanitarian Use Device

ATTACHMENT A

Institutional Review Board (IRB) Information

1. Please Provide the FWA Number assigned to the IRB that oversees clinical trial activities within your Institution:

   FWA Number: _____

   No further information is necessary if an FWA Number is provided.

2. ***If your Institution does not have an FWA Number***, please provide the following information:

a. The IRB name, if any, used by the institution or organization (e.g., State University Behavioral IRB or University Healthcare Biomedical IRB):

   _____

b. Complete Mailing Address of the IRB, including City, State and Zip; plus country if outside the USA:

   _____

   _____

   _____

   _____

c. Telephone Number(s) for IRB:

   _____

   _____

d. Fax Number for IRB:

   _____

e. IRB Chairperson

a. Full Name: _____
b. Title or Position: _____
c. Earned Degree(s): _____

f. In lieu of providing IRB Member information in the table below, the Chairperson of the IRB may attest that the IRB is duly constituted and complies with 21 CFR parts 50 and 56. Links are as follows:

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56&showFR=1

As Chairperson for the Institutional IRB referenced above in Section 2, I attest that our Institutional Review Board complies with the FDA 21 CFR Parts 50 and 56.

RESEARCH INSTITUTION _____

DATE: _____

READ AND ACKNOWLEDGED:

INSTITUTIONAL REVIEW BOARD CHAIRMAN: (PRINT NAME) _____

INSTITUTIONAL REVIEW BOARD CHAIRMAN (SIGNATURE) _____

If section 2.f. is <u>not</u> completed by the Chairman, please complete the table below to identify all IRB Members approving the use of the CliniMACS® CD34 Reagent System as a Humanitarian Use Device:

Member Name (Last, First)	Earned Degree(s)	Scientist (S) or Nonscientist (N)	Primary Scientific or Nonscientific Specialty	Affiliation with Institution(s) Y/N
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				

Please return this form to your Clinical Applications Manager, or Fax to 1-831-417-9621

Attachment B

(On Institutional Letterhead)

Notice of IRB Approval for the CliniMACS® CD34 Reagent System as a Humanitarian Use Device

Date:

Miltenyi Biotec Incorporated
85 Hamilton Street
Cambridge, MA 02139
Phone: 617-218-0030
Fax: 1-831-417-9621

Regarding: IRB Approval of the CliniMACS® CD34 Reagent System as a Humanitarian Use Device

To Whom It May Concern:

The letter certifies that the CliniMACS® CD34 Reagent System has been reviewed and approved by our Institutional Review Board (IRB) for Use as a Humanitarian Use Device. During the review of this Project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

It is agreed that any and all adverse event(s) that occur when using the CliniMACS® CD34 Reagent System will be reported in accordance with the Medical Device Reporting Regulations, including notification to Miltenyi Biotec Incorporated at the address and/or fax number listed above.

Signed: _____

Print Name: _____

IRB Chairman or Treating Physician: _____

Institution: _____

Address: _____

_____

_____

Email Address: _____

Phone: _____

CliniMACS® CD34 Reagent System

Rx only

For *in vitro* use only.

HUMANITARIAN DEVICE:

Authorized by U.S. Federal law for use in the treatment of patients with acute myeloid leukemia (AML) in first complete remission. The effectiveness of the device for this use has not been demonstrated.

MANUFACTURED BY:
Miltenyi Biotec GmbH
Friedrich-Ebert-Straße 68
D 51429 Bergisch Gladbach | Germany
Phone: +49 2204 8306-80
Fax:+49 2204 85197

DISTRIBUTED IN THE US BY:
Miltenyi Biotec Inc.
2303 Lindbergh Street | Auburn, CA 95602
Phone: 1 800 367 6227

INDICATIONS FOR USE

The CliniMACS® CD34 Reagent System is indicated for processing hematopoietic progenitor cells collected by apheresis (HPC, Apheresis) from an allogeneic, HLA-identical, sibling donor to obtain a $CD34^+$ cell-enriched population for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional graft versus host disease (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) in first morphologic complete remission.

CONTRAINDICATIONS

Do not use $CD34^+$ cells prepared with CliniMACS® CD34 Reagent System in patients with known hypersensitivity to murine (mouse) proteins or iron-dextran.

DESCRIPTION

The CliniMACS® CD34 Reagent System is a medical device system that consists of the following components:

- CliniMACS® CD34 Reagent - dark amber, non-viscous, colloidal solution containing an antibody conjugate in buffer. The conjugate consists of a murine IgG_1 monoclonal antibody directed against the Class II epitope of the human CD34 antigen, which is chemically conjugated to dextran beads having an iron oxide/hydroxide core. (See the CliniMACS® CD34 Reagent Package Insert for more information.)
- CliniMACS® plus Instrument - software-controlled instrument that processes the HPC, Apheresis. (See the CliniMACS® User Manual for the CD34 Reagent System for more information.)
- CliniMACS® Tubing Set TS or Tubing Set LS - a single-use, sterile, disposable tubing set with two proprietary cell separation columns. The CliniMACS® Tubing Set TS is for processing HPC, Apheresis preparations containing up to 0.6×10^9 $CD34^+$ cells out of a total cell number not exceeding 60×10^9 white blood cells. The CliniMACS® Tubing Set LS is for larger scale preparations containing up to 1.2×10^9 $CD34^+$ cells out of a total cell number not exceeding 120×10^9 white blood cells. (See the CliniMACS® Tubing Sets Package Insert and the CliniMACS® User Manual for the CD34 Reagent System for more information.)
- CliniMACS® PBS/EDTA Buffer - a sterile, isotonic phosphate-buffered, 1 mM EDTA, saline solution, used as external wash and transport fluid for the *in vitro* processing of HPC, Apheresis. (See the CliniMACS® PBS/EDTA Buffer Package Insert and the CliniMACS® User Manual for the CD34 Reagent System for more information.)

PRINCIPLES OF OPERATION

The CliniMACS® CD34 Reagent System is an *in vitro* medical device system used to select and enrich $CD34^+$ cells from HPC, Apheresis while passively depleting other cells, such as $CD3^+$ T cells, which cause graft versus host disease. The system is based on "magnetically-activated cell sorting" (MACS) employing antibodies conjugated to iron-containing particles that can be attracted to a magnetic field (referred to as "magnetic labeling"). Using the specificity of anti-CD34 antibody interaction with cell surface CD34 antigen found on hematopoietic progenitor cells, the system enriches $CD34^+$ cells from HPC, Apheresis by passing the antibody-labeled cell suspension through a separation column with a strong magnetic gradient. The separation column retains the magnetically labeled $CD34^+$ target cells while unlabeled cells flow through and are collected in the Negative Fraction Bag. Several automated washing steps are performed, disposing most of the liquid into the Buffer Waste Bag. The magnetically-selected $CD34^+$ cells are released from the separation column when the magnet is disengaged, removing the magnetic field, and the target $CD34^+$ cells are eluted into the Cell Collection Bag.

WARNINGS

- Do not infuse the CliniMACS® CD34 Reagent or the CliniMACS® PBS/EDTA Buffer into patients directly.
- Hypersensitivity Reactions

  Hypersensitivity reactions, including anaphylaxis, have been observed during infusion of $CD34^+$ cells from the CliniMACS® CD34 Reagent System. Monitor the patient for hypersensitivity reactions, including anaphylaxis, during infusion of $CD34^+$ cells from the CliniMACS® CD34 Reagent System.
- Engraftment failure

  Failure to infuse an adequate number of functioning $CD34^+$ cells can result in engraftment failure. Collect sufficient HPC, Apheresis to yield at least 2.4×10^6 $CD34^+$ cells per kg of patient body weight after system processing (see Device Performance below). The clinical trial (see Clinical Performance below) using the CliniMACS® CD34 Reagent System to process HPC, Apheresis did not test allografts with less than 2.4×10^6 $CD34^+$ cells per kg of recipient body weight. Monitor patients for laboratory evidence of hematopoietic recovery after transplantation.
- Acute and chronic graft versus host disease (GVHD)

  GVHD can occur in patients who receive HPC, Apheresis processed using the CliniMACS® CD34 Reagent System. Use pharmacologic prophylaxis if more than 1×10^5 $CD3^+$ cells per kilogram of recipient body weight are infused.
- Delayed immune reconstitution after transplantation

  Removal of T cells from the HPC, Apheresis can delay immune reconstitution after transplantation. Patients who receive the $CD34^+$ cell-enriched population prepared using the CliniMACS® CD34 Reagent System are at risk for serious opportunistic viral infections, including post-transplant lymphoproliferative disorder caused by Epstein-Barr virus (EBV) and cytomegalovirus (CMV). Monitor for EBV and CMV in the peripheral blood of patients after transplantation and initiate appropriate treatment promptly.

PRECAUTIONS

- Safety and probable benefit in children under the age of 17 years have not been established.
- Drugs may be incompatible with the CliniMACS® PBS/EDTA Buffer. Do not add drugs to the buffer other than Human Serum Albumin as specified in the CliniMACS® User Manual for the CD34 Reagent System.
- Do not use cryopreserved and thawed HPC, Apheresis because cryopreservation promotes cell clumping, which may lead to device performance issues. Process HPC, Apheresis as soon as available, but not longer than 24 hours after collection.
- Use only HPC, Apheresis from an allogeneic, HLA-identical sibling donor with the CliniMACS® CD34 Reagent System.
- Collect HPC, Apheresis according to standard hospital or institutional leukapheresis procedures in standard leukapheresis collection bags. Do not include additional anticoagulants or blood additives, such as heparin, other than those normally used during leukapheresis. Keep the HPC, Apheresis at controlled room temperature (+19 °C to +25 °C (67° to 77° F)) if it has to be stored, e.g., overnight, before processing. Do not allow the concentration of leukocytes to exceed 0.2×10^9 cells per mL.
- Only trained operators should use the CliniMACS® CD34 Reagent System to prepare $CD34^+$ cells for infusion. Operator training is provided by Miltenyi Biotec authorized personnel.

PROCEDURES

Refer to the CliniMACS® User Manual for the CD34 Reagent System for complete instructions. An on-line version is available at www.cd34-aml.com/usermanual.

Do not connect the CliniMACS® CD34 Reagent System to the patient at any time.

Collect the following data on the leukapheresis product before starting the preparation of the HPC, Apheresis for enrichment:

- Total number of leukocytes
- Percentage of $CD34^+$ cells
- Total number of $CD34^+$ cells
- Percentage of $CD3^+$ cells
- Total number of $CD3^+$ cells
- Viability

The $CD34^+$ cells are enriched in the following four steps:

Step 1 - Immunomagnetic Labeling of $CD34^+$ Hematopoietic Progenitor Cells

Add the CliniMACS® CD34 Reagent to the HPC, Apheresis and allow the reagent to bind to the $CD34^+$ cells. After incubation, remove unbound reagent from the suspension. The cells are now ready for selection in an automated continuous flow selection process using the CliniMACS® plus Instrument.

NOTE: Exceeding the capacity for either total cell number or $CD34^+$ cell number may impact the performance of the device. The standard-scale capacity for the enrichment of $CD34^+$ cells using the CliniMACS® CD34 Reagent System with one vial of CD34 Reagent and the CliniMACS® Tubing Set TS is 0.6×10^9 $CD34^+$ cells out of a total cell number not exceeding 60×10^9 cells. Large-scale capacity for the enrichment of up to 1.2×10^9 $CD34^+$ cells out of a total cell number of 120×10^9 cells (large-scale application) requires two vials of the CliniMACS® CD34 Reagent and the CliniMACS® Tubing Set LS.

Step 2 - Choice of Program

Choose CD34 Selection 1/2 program on the CliniMACS® plus Instrument.

Step 3 - Installation of Tubing Set

- Install tubing set (TS or LS).
- Attach Cell Collection Bag to the tubing set.
- Follow the prompts provided on the CliniMACS® plus Instrument screen to complete the tubing set installation.
- Join the bag containing the cells from Step 1 to the sterile CliniMACS® Tubing Set.

Step 4 - Selection of CD34$^+$ Cells

Process the cells through the CliniMACS® plus Instrument using the CD34 Selection program. The instrument selects cells by passing the immunomagnetically-labeled suspension through the separation column, in which strong magnetic gradients are generated. The separation column retains the immunomagnetically-labeled CD34$^+$ target cells while unlabeled cells flow through and are collected in the Negative Fraction Bag. Automated washing steps dispose of excess liquid into the Buffer Waste Bag. The retained CD34$^+$ cells are released from the separation column when the magnet is disengaged, and the target CD34$^+$ cells are eluted into the Cell Collection Bag.

Establish the suitability of the target CD34$^+$ cells before infusion. Examine the following parameters:

- Total number of leukocytes
- Total viability
- Total number of CD34$^+$ cells
- Total number CD3$^+$ cells
- Purity and recovery of CD34$^+$ cells
- CD3 log depletion

See Table 1 for performance values observed in the clinical trial.

Assessment of the non-target fraction for the total number and viability of leukocytes is recommended to assess the performance of the device and quality of the device output (CD34$^+$ cells).

DO NOT infuse the CD34$^+$ cells in CliniMACS® PBS/EDTA Buffer! Exchange the CliniMACS® PBS/EDTA Buffer contained in the CD34$^+$ target fraction to a clinical grade infusion solution appropriate for infusion into humans prior to infusion of the CD34$^+$ cells.

See the CliniMACS® User Manual for the CD34 Reagent System for full instructions. The CliniMACS® User Manual for the CD34 Reagent System includes instructions on the preparation of solutions and samples, as well as a detailed list of equipment and materials that are required for CD34$^+$ cell selection. (See Chapter 3 of the CliniMACS® User Manual for the CD34 Reagent System.)

PERFORMANCE CHARACTERISTICS

Adverse Reactions

The safety of the CliniMACS® CD34 Reagent System was evaluated in a clinical trial that included 44 subjects with AML undergoing HPC, Apheresis transplantation from an HLA-identical sibling donor.[1] There were 16 males and 28 females of median age 49 years (range, 21 to 60 years). The myeloablative preparative regimen included total body irradiation, thiotepa, cyclophosphamide, and rabbit antithymocyte globulin. The median number of CD34$^+$ cells infused was 7.9×10^6 per kg (range 2.4 to 30.4). The median number of CD3$^+$ cells infused was 0.07×10^5 per kg (range 0.01 to 0.83).

Among the 44 subjects, there were no grades 3 to 5 infusion reactions, no allergic reactions, and no graft failures. Testing for development of human anti-mouse antibodies (HAMA) was not performed. A severe or life-threatening infection was reported for 38% of the subjects. An infection by any virus was reported for 61% of the subjects, and the 1-year incidence of EBV infection in particular was 25%. One subject (2%) developed a fatal post-transplantation lymphoproliferative disorder.

Device Performance

The safety and feasibility of use of the CliniMACS® CD34 Reagent System was evaluated in a multicenter, single-arm, clinical trial. In this study, allogeneic donors were mobilized with daily subcutaneous granulocyte colony-stimulating factor (G-CSF) at a dose of 10 to 16 µg per kg per day. Leukapheresis was performed on a continuous flow cell separator commencing on Day 5 of G-CSF treatment, and CD34$^+$ cell enrichment of the HPC, Apheresis was performed using the CliniMACS® CD34 Reagent System. Most donors underwent at least two, but not more than three, apheresis to reach the post-selection enrichment target of greater than 5.0×10^6 CD34$^+$ cells per kg recipient body weight while maintaining less than 1.0×10^5 CD3$^+$ cells per kg recipient body weight.

Eighty-four selection procedures were performed on HPC, Apheresis collected from a total of 44 donors. The minimum number of CD34$^+$ cells required for transplantation, greater than 2×10^6 per kg recipient body weight, was achieved for 100% (44) of donors. This was attained with one apheresis for 93% (41) of the donors and two apheresis for an additional 7% (3). The target number of CD34$^+$ cells, greater than 5×10^6 per kg recipient body weight, was achieved for 84% (37) of the 44 donors. This target number was attained with one apheresis for 36% (16), with two apheresis for 45% (20), and with three apheresis for 2% (1) of the 44 donors. Device performance is shown in the table below.

Table 1: Device Performance Summary; N=84

Attributes Measured		Mean	Std Dev	Median	Min	Max
Starting TNC $\times 10^{10}$		7.46	3.26	6.95	2.1	18.0
Initial Viability (%)		97.60	2.74	99.0	86.9	100.0
CD34$^+$ Cells $\times 10^7$	Starting Count	59.71	41.09	47.85	7.3	208.0
	Final Count	36.90	25.05	29.80	6.1	119.0
Final CD34$^+$ Yield (%)		66.06	20.25	65.00	29.9	125.6
Final CD34$^+$ Purity (%)		93.03	8.31	96.65	61.5	99.8
CD3$^+$ T Cells $\times 10^8$	Starting Count	179.45	69.80	168.50	55.00	362.00
	Final Count	0.00652	0.01039	0.00217	0.00026	0.04971
Log_{10} CD3$^+$ T-Cell Depletion		4.78	0.55	4.90	3.2	5.9
Final Viability (%)		96.57	3.84	97.70	74.0	100.0
Total CD34$^+$ Cells Infused/kg $\times 10^6$		8.81	5.21	7.924	2.41	30.360
Total CD3$^+$ Cells Infused/kg $\times 10^6$		0.015	0.020	0.0066	0.0011	0.08328

Clinical Performance

The clinical trial included 37 subjects with AML in first complete remission (CR) undergoing transplantation. All donors were HLA-identical siblings. The study subjects included 14 (37.8%) males and 23 (62.2%) females of median age 48 years (range: 21 to 60 years). The cytogenetics risk group was intermediate for 68%, unfavorable for 27%, and unknown for 5% of subjects. The myeloablative preparative regimen included total body irradiation, thiotepa, cyclophosphamide, and rabbit antithymocyte globulin. The median number of CD34$^+$ cells infused was 7.4×10^6 per kg recipient body weight (range: 2.4 to 30.4). The median number of CD3$^+$ cells infused was 0.07×10^5 per kg recipient body weight (range: 0.01 to 0.63). No immunosuppressive drugs were administered for prevention of GVHD.

All subjects achieved an absolute neutrophil count that exceeded 0.5×10^9 per liter by Day 21 after transplantation. The platelet count recovered to greater than 20×10^9 per liter by Day 100 for 91.9% (95% CI, 82.4 to 100%). There was one late graft failure. At Day 100 after transplantation, the cumulative incidence of grades 2 to 4 acute GVHD was 27% (95% CI, 14 to 42%), and that for grades 3 to 4 acute GVHD was 5% (95% CI, 1 to 16%). The cumulative incidence of chronic GVHD at 2 years after transplantation was 19% (95% CI, 8 to 33%).

Additional Safety Assessment

The potential risks of using the CliniMACS® CD34 Reagent System were evaluated via a Data Analysis Protocol (DAP), which retrospectively compared the Day-100, 1-year, and 2-year endpoints in the clinical trial to the same endpoints as had been measured in a historical control group of patients that had used a conventional pharmacologic method of GVHD prophylaxis. Table 2 shows the results of the comparison.

Table 2: Comparison of the Single-Arm CliniMACS® CD34 Reagent System Study to historical controls using pharmacological immunosuppression

Endpoints	Single-Arm CliniMACS® CD34 Reagent System (n=37) % (95% CI)	Historical Controls Using pharmacological immunosuppression (n=65) % (95% CI)
% Neutrophil Engraftment at Day 30 (>500/µL)*	100	100$^+$
% Platelet Engraftment at Day 30 (>20,000/µL)*	92 (82.4, 100)	84$^\#$(72.5, 91.4)
Acute GVHD at Day 100, Grades 2–4*	27 (13.9, 42.0)	35 (23.9, 47.0)
Acute GVHD at Day 100, Grades 3–4*	5 (1, 16.1)	9 (3.7, 17.8)
Chronic GVHD at 2 years*	19 (8.2, 33.0)	49 (36.5, 61.0)
Relapse Rate at 2 years*	16 (6.5, 29.9)	28 (17.7, 39.7)
Non-relapse Mortality at 2 years*	20 (8.5, 34.5)	14 (6.8, 23.4)
Overall Survival at 2 years	67 (48.8, 79.7)	67 (54.1, 77.2)
Disease-free Survival at 2 years	64 (46.0, 77.4)	58 (44.8, 68.9)
GVHD-free Survival at 2 years	46 (29.6, 60.9)	18 (9.6, 28.2)

* Cumulative Incidence
$^+$ neutrophil engraftment data missing for two patients
$^\#$ Platelet data missing for one patient

REFERENCES

1 Devine SM, Carter S, Soiffer RJ, Pasquini MC, Hari PN, Stein A, Lazarus HM, Linker C, Stadtmauer EA, Alyea EP 3rd, Keever-Taylor CA, O'Reilly RJ. Low Risk of Chronic Graft-versus-Host Disease and Relapse Associated with T Cell-Depleted Peripheral Blood Stem Cell Transplantation for Acute Myelogenous Leukemia in First Remission: Results of the Blood and Marrow Transplant Clinical Trials Network Protocol 0303. Biology of Blood and Marrow Transplantation 2011;17:1343-1351.